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Aluminum Toxicity Following Intravesical Alum Irrigation for Hemorrhagic Cystitis

Vikramjit S. Kanwar, MRCP, Jesse J. Jenkins III, MD, Belinda N. Mandrell, CPNP, and Wayne L. Furman, MD

Mental status changes in an immunosuppressed child can be due to a variety of causes; aluminum toxicity is rarely considered. We report a teenage girl with acute lymphoblastic leukemia who developed mental status changes, speech disturbance, coarse tremor, and abnormal EEG findings following intravesical 1% alum irrigation and administration of aluminum-containing antacids. Her serum aluminum levels were mildly elevated (14–22 μg/L, normal 0–6 μg/L), and bone marrow biopsy specimens demonstrated aluminum deposition on special staining (Krueger's method). All abnormalities resolved after a nine-week course of intravenous deferoxamine.

Key words: children, leukemia, aluminum, alum, toxicity, cystitis, encephalopathy

INTRODUCTION

Aluminum toxicity is well-documented in pediatric nephrology patients who have received aluminum-rich antacids or dialysis fluid [1], but is rarely encountered by pediatric oncologists. Although clinical manifestations include microcytic hypochromic anemia and osteomalacia, the most dramatic symptoms are usually neurologic [2]. Recently, two children receiving intravesical alum irrigation for hemorrhagic cystitis developed acute encephalopathy secondary to aluminum intoxication [3,4].

Here, we report a teenage girl who developed abnormal neurologic and EEG findings following intravesical 1% alum irrigation and administration of aluminum-containing antacids. Elevated serum aluminum levels and bone marrow biopsy special stains confirmed the diagnosis of aluminum toxicity. Administration of intravenous deferoxamine (DFO) was associated with a complete recovery.

CASE REPORT

A 15-year-old girl, diagnosed at St. Jude Children's Research Hospital with acute lymphoblastic leukemia in November 1991, received multi-agent chemotherapy as previously described [5] for 18 months. She then suffered a bone marrow relapse and was administered salvage chemotherapy [6], that included two cycles of cyclophosphamide (cumulative dose, 3 g/m^2) and mitoxantrone (36 mg/m^2). One week after the second cycle, she was hospitalized with fever and pancytopenia. On admission, she was given broad-spectrum antibiotics and amphotericin-B. Four weeks after hospitalization, a 10-day course of acyclovir was administered for herpes zoster. No significant bacterial or fungal infection was isolated, and all antibiotics were discontinued after 11 weeks.

Gross hematuria began 2 weeks after admission and persisted for 8 weeks, requiring transfusion of 43 units of packed red cells and 47 units of pheresed single-donor platelets. A Foley catheter was inserted 1 week after onset of hematuria, and the patient received 32.1 liters of intravesical 1% alum (ammonium aluminum sulfate) irrigation over 12 days; she was thus exposed to 19 grams of aluminum by this route. Persistent hematuria led to administration of 11 days of intravenous ribavirin for adenovirus-positive urine cultures [7]; the hematuria eventually resolved following embolization of the left vesical artery.

Two weeks after completion of intravesical alum irrigation, the patient manifested unusual behavior with euphoria, eye-rolling, and lip-smacking. On examination,

From the Departments of Hematology-Oncology, (V.S.K., B.N.M., W.L.F.), and Pathology and Laboratory Medicine, (J.J.J.), St. Jude Children's Research Hospital, Memphis, and the Department of Pediatrics, University of Tennessee, Memphis, College of Medicine, Memphis, Tennessee.

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Address reprint requests to Dr. Vikramjit S. Kanwar, Department of Hematology-Oncology, St. Jude Children's Research Hospital, P.O. Box 318, Memphis, TN 38101-0318.

her temperature was 39.8°C, pulse 137/min, respiratory rate 20/min and blood pressure 116/70 mmHg. Physical examination revealed alopecia, a subcutaneous port in the left chest, and old zoster lesions. Changes in mental status included decreased short-term memory and nominal aphasia; orientation in time and space was preserved. The results of cranial nerve and sensory examinations were normal; motor examination revealed coarse tremor, dysarthria, and hesitancy. Deep tendon reflexes were present and symmetrical.

A CT scan of the brain was normal, and CSF examination demonstrated a white cell count of 1/mm^3, (20% lymphocytes, 10% monocytes, and 70% histiocytes on cytospin), protein 36 mg/dL, and glucose 148 mg/dL; viral, bacterial, and fungal cultures were negative. Other investigations were as follows: hemoglobin 9.8 g/dL, white blood count 200/μL, and platelet count 33,000/μL; serum electrolytes: sodium 138 mEq/L, potassium 3.8 mEq/L, chloride 98 mEq/L, bicarbonate 30 mEq/L, BUN 20 mg/dL, creatinine 0.9 mg/dL, and glucose 179 mg/dL; liver function tests: serum bilirubin 3.8 mg/dL, alkaline phosphatase 134U/L, ALT 54U/L, and serum ammonia 42 μmol/L; thyroid function tests: thyroxine 5.7 μg/dL (normal 4.2–13.6 μg/dL), and free T4 index 6.1 μg/dL (normal 4.2–13.0 μg/dL).

Neurologic symptoms were initially attributed to intravenous Dilaudid, which was administered for bladder spasm. Accordingly, the patient was weaned off all intravenous narcotic agents. Symptoms persisted, and although an MRI performed 1 week later was normal, an EEG showed diffuse bilateral slowing with bursts of fast activity. A serum aluminum level of 14 μg/L (normal 0–6 μg/L) was documented; 2 weeks later, this had risen to 22 μg/L. The diagnosis of aluminum toxicity was thus confirmed.

A review of medications showed that the patient had received 18g of aluminum in the form of antacids (Maalox, Rhone-Poulenc Rorer, PA, and Mylanta, Johnson & Johnson, Merck, PA) administered since admission for epigastric discomfort. These agents were discontinued and the patient received intravenous DFO (40 mg/kg/dose, alternate-day) for 9 weeks. Bone marrow biopsies obtained during this period stained positively for aluminum by Krueger's method [8] (Fig. 1). Clinical symptoms, serum aluminum levels, and bone marrow biopsy findings normalized following DFO therapy. The patient currently remains well and in remission.

DISCUSSION

Hemorrhagic cystitis can be life-threatening in children with cancer. Its treatment has included aminocaproic acid, surgical cauterization, hypogastric artery ligation, and intravesical instillation of formalin, silver nitrate, or alum [9]. Although the safety of alum irrigation has been emphasized [10–12], five patients, including two children, have developed acute aluminum toxicity following its use. In fact three patients, including one child, have died [3,4,13–15] (Table I).

All cases of toxicity previously reported with intravesical alum therapy [3,4,13–15] displayed acute neurologic deterioration, unlike our patient who presented with delayed onset of dementia. We considered a wide differential diagnosis [16]: cerebral tumor or abscess, viral encephalitis, fungal meningitis, hepatic or renal failure, hypercalcemia, hypoglycemia, hyperosmolar non-ketotic coma and drug intoxication. Aluminum-induced neurotoxicity is rare [2], and was not initially considered even though our patient displayed nominal aphasia, loss of short-term memory, confabulation, dysarthria, coarse tremor, poor coordination and hesitancy.

One week after symptoms first appeared, the patient's serum aluminum level as measured by mass spectrometry was found to be elevated. The EEG also documented multifocal bursts of slow and spike activity superimposed on a normal background, which Alfrey [17] described as a diagnostic finding in aluminum-induced encephalopathy. Bone marrow biopsy specimens taken at initiation of chelation therapy and stained by Kreuger's method [8], revealed a red-purple line along the trabecular bone mineralization front, considered characteristic for aluminum deposition (Fig. 1).

The diagnosis of aluminum toxicity is usually based on clinical suspicion and characteristic EEG changes [17]. Serum aluminum levels, as measured by mass spectrophotometry, help to confirm this diagnosis, but the relationship between toxicity and serum levels is not always clear. Andreoli and colleagues [18], reported a series of pediatric patients with aluminum-related encephalopathy, all of whom had serum aluminum levels in excess of 100 μg/L at diagnosis. On the other hand, Bozynski et al. [19] documented toxicity in two children with serum aluminum levels of 25–50 μg/L, Altmann et al. [20] demonstrated psychomotor abnormalities in 27 patients with a mean serum aluminum level of 59 ± 9 μg/L, and Kavoussi et al. [14] reported marked neurologic changes in an elderly patient whose serum aluminum level was only 17 μg/L.

Patients exposed to intravesical alum who developed aluminum toxicity had acute neurologic deterioration which occurred during therapy [3,4,13–15] (Table I). We hypothesize that our patient's delayed sub-acute presentation resulted from progressive tissue loading with aluminum from both oral and intravesical routes. Our patient was exposed to 32.1 liters of 1% alum irrigation fluid (19g aluminum). Dalton et al. have reported significant resorption of cytotoxic drugs through bladder urothelium, with urothelial damage enhancing this effect seven to eight-fold [21]. We postulate that a breach of urothelial integrity secondary to hemorrhagic cystitis allowed alu-

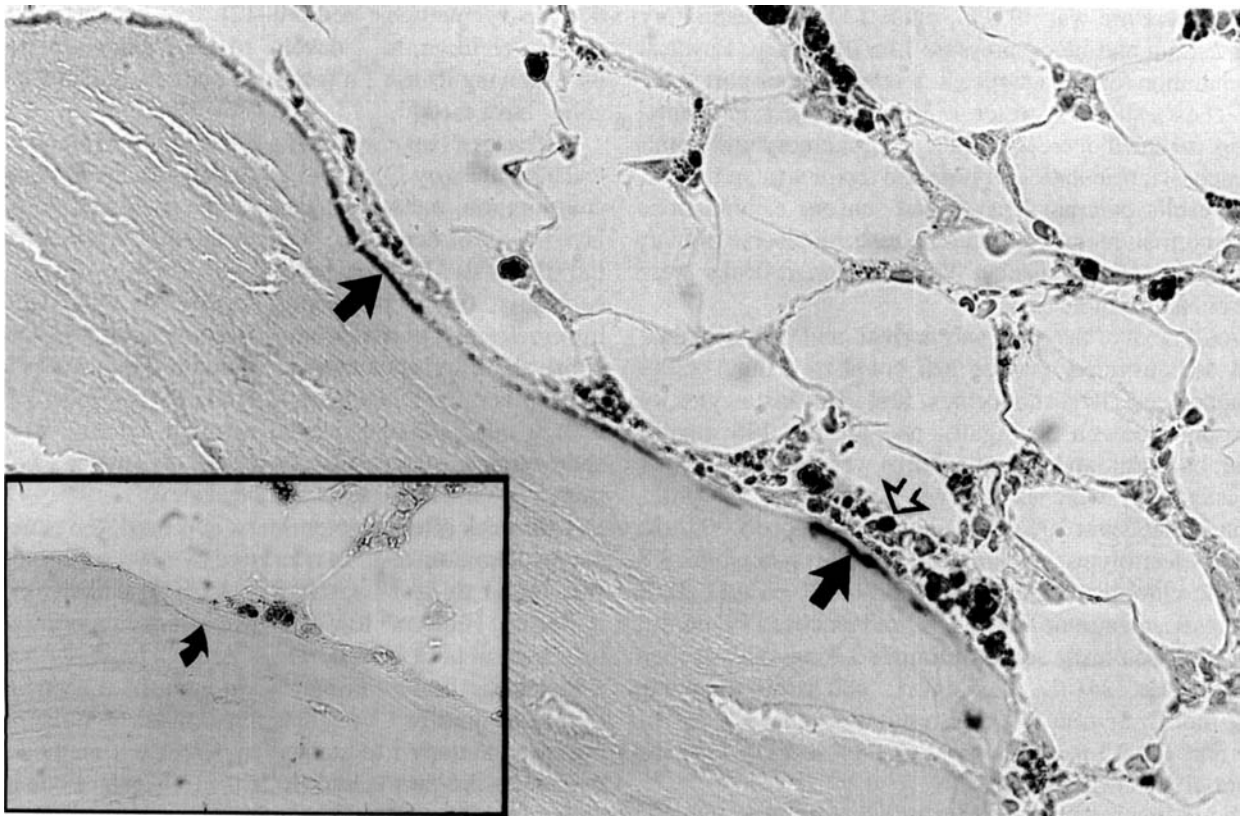

Fig. 1. Bone marrow biopsies performed at commencement and completion of deferoxamine therapy. Aluminum deposition is visible as a red-purple line at the mineralized trabecular bone boundary (solid arrows) and is distinguished from the coarsely granular brown staining of iron in the marrow macrophages (open arrow). At completion of therapy **(inset),** no staining is present at the mineralized trabecular bone boundary (curved arrow) while brown iron staining is still present in marrow macrophages. Krueger's method for aluminum, 100× original magnification.

TABLE I. Aluminum Toxicity Following Intravesical Alum Irrigation

Age/ sex	Primary diagnosis	Al[a] dose (g)	Signs and symptoms of Al toxicity	Highest measured serum Al Conc[b] (μg/L)	Outcome	Chelation therapy	Reference
4M	Rhabdomyosarcoma	1.89	Coma, slow wave EEG	135	Survived	No	Moreno et al. [3]
15F	Acute leukemia	37	Memory loss, aphasia, tremors	22	Survived	Yes	Kanwar et al. [this report]
17F	Rhabdomyosarcoma	NA[c]	Encephalopathy, cardiomyopathy	258	Died	No	Seear et al. [4]
31F	Lymphoma	61.5	Coma, myoclonus	436	Died[d]	Yes	Perazella & Brown [15]
74M	Prostate carcinoma	16	Coma, abnormal EEG	17	Survived	No	Kavoussi et al. [14]
87M	Bladder carcinoma	5.7	Coma	210	Died	No	Shoskes et al. [13]

[a]Al = aluminum.
[b]Conc = concentration.
[c]NA = not available.
[d]Secondary to intracerebral bleed.

minum to leach across vesical mucosa, contributing significantly to tissue loading. Perazella and Brown [15] reported a patient who received one course of alum irrigation uneventfully, only to develop acute toxicity after a second course. Administration of aluminum-containing antacids contributed a further 18g of aluminum: it is not possible to say which route of administration contributed most to the toxicity observed.

The mechanism of aluminum-related neurotoxicity is unknown. However, we do know that aluminum accumulation in cerebral gray matter is associated with decreased synaptosomal uptake of GABA, glycine, and glutamic

acid [2]. Although severe dementia may be refractory to therapy [22], early neurologic changes are apparently reversible either with [17,19,23], or without [14,15] DFO therapy. Alfrey stressed the importance of early intervention with chelation therapy [17], and we therefore administered intravenous DFO (40 mg/kg) on alternate days for 9 weeks until the aluminum level normalized and the patient's symptoms resolved. Transient clinical deterioration has been reported when aluminum is mobilized from body stores [2]; however, we did not observe this.

In conclusion, aluminum toxicity should be considered in all patients with hemorrhagic cystitis who develop unusual neurologic symptoms following intravesical alum irrigation. This mode of therapy should be applied with caution to patients who have renal impairment; similarly, all aluminum-containing medications should be discontinued prior to initiating therapy. Due to poor correlation with clinical toxicity and delayed availability of results, serum aluminum level testing remains of limited value: a high index of clinical suspicion is thus mandatory. In patients diagnosed with toxicity, intravenous DFO may be of therapeutic benefit.

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